Corres. and Mail
BOX AF

AF

#13

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Jacques DEGELAEN et al.	:	Docket No.00292/Case 16.72.US
Serial No. 09/276,923	:	Group Art Unit 1645
Filed March 26, 1999	:	Examiner R. Zeman

PROCESS FOR DETERMINING ANTIBIOTICS CONTAINING A B-LACTAM RING IN A BIOLOGICAL FLUID

RESPONSE UNDER 37. CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1645

JM
12/5/01

REQUEST FOR RECONSIDERATION OF FINAL REJECTION

Assistant Commissioner for Patents,
Washington, D.C.

Sir:

This is responsive to the Official Action dated September 6, 2001.

Favorable reconsideration is respectfully requested in view of the following remarks.

The pending claims are claims 16-36. Claims 28-36 have been withdrawn from consideration by the Examiner. Claims 16-27 remain rejected under a single 35 U.S.C. §103 rejection.

Applicants confirm the Examiner's presumption to be correct in that the subject matter of the various claims was commonly owned at the time the invention was made for purposes of 35 U.S.C. §103(c) and 35 U.S.C. §102(f)/(g).

Claims 16-27 were rejected under 35 U.S.C. §103(a) over Piasio (USPN 5,434,053) in view of either Joris et al. (FEMS Microbiology Letters Vol. 70, 1990, pages 107-114) or Zhu et al. (Journal of Bacteriology, Vol. 172, No. 2, February 1990, pages 1137-1141). Applicants respectfully traverse this rejection.

Before addressing this rejection, Applicants believe that it would be beneficial to describe the claimed invention.

The present invention, as embodied in the instant claims, is drawn to a process for detecting antibiotics which contain a β-lactam ring in a biological fluid wherein a determined volume of the fluid is placed in contact with a recognition agent to form a mixture, incubating the mixture to allow for formation of a complex between the antibiotic to be detected and the recognition agent, placing the mixture in contact with a reference antibiotic which has been immobilized on a solid support under conditions allowing for the formation of a complex between the reference antibiotic and any recognition agent which has not yet been complexed with the antibiotic, and detecting the antibiotic by determining the amount of recognition agent which is complexed to the reference antibiotic. The recognition agent contains a receptor obtained from *Bacillus licheniformis* which specifically binds to antibiotics having a β-lactam ring. The amount of recognition agent which has been complexed with the reference antibiotic is inversely proportional to the amount of antibiotics present in the biological fluid.

The receptor in the recognition agent can be a BlaR receptor or a BlaR-CTD receptor which may be coupled to a labeling agent selected among various colloidal particles and/or may contain a fluorescent substance, may be an enzyme or may be chemically coupled to an enzyme.

The technical problem solved by the present invention is to provide an alternative test method to those in the prior art which is much more rapid and has improved sensitivity to detection of antibiotics containing a β-lactam ring in comparison to existing tests such as Piasio.

Piasio discloses a test designed to detect low levels of antibiotics in liquid media such as milk, urine or blood. The time required for the test in Piasio should not exceed about 15 minutes. (Piasio, column 1, lines 42-59) Piasio discloses detecting a wide range of antibiotics such as β-lactams, tetracyclines, gentamycine, sulpha compounds or combinations thereof in biological fluids. This method comprises contacting the test fluid with an amount of a recognition agent (antibiotic binding protein), contacting the resulting mixture with a reference antibiotic immobilized on a solid support and determining the amount of recognition agent bound to the immobilized reference antibiotic.

Piasio discloses the recognition agents to be obtained from antibiotic-sensitive microorganisms, such as *Bacillus stearothermophilus, Bacillus subtilis, Streptococcus* thermophilus or *Escherichia coli*, preferably *Bacillus stearothermophilus*.

However, as opposed to the present claimed inventive method, Piasio does not disclose using a recognition agent obtained from *Bacillus licheniformis*. This is even acknowledged by the Examiner (page 7 of the Office Action) which states that "Piasio differs from the instant invention in that it does not explicitly disclose the use of B1aR or B1aR-CTD, or any other proteins obtained from *Bacillus licheniformis*."

In addition, the best disclosed example in Piasio uses a *Bacillus stearothermophilus* binding protein which detects 5 ppb of benzyl penicillin after an incubation time of 8 minutes.

To the contrary, the present invention, as stated above, provides a superior alternative test which is more rapid than Piasio and has improved sensitivity by choosing binding agents from *Bacillus licheniformis* instead of those disclosed in Piasio. Applicants have thus obtained experimental results showing detection of less than 4 ppb of penicillin in 3 minutes. (See e.g., lines 8-13 on page 16 of the present specification)

Consequently, the selection of binding agents obtained from *Bacillus licheniformis* provides an improved method of detection with superior properties in terms of time and sensitivity. Although Piasio does disclose, as stated by the Examiner, the use of any antibiotic binding agent which can be obtained from an antibiotic-sensitive microorganism, Piasio does not disclose or suggest using *Bacillus licheniformis* nor does Piasio provide any motivation whatsoever for selecting binding agents obtained from *Bacillus licheniformis* which provide the shown enhanced properties of the present claimed invention.

The Examiner alleges (on pages 7 and 8) that Joris and Zhu teach the increased binding efficiencies of the concerned *Bacillus licheniformis* proteins. However, the Examiner fails to cite any specific paragraph to support this allegation. Such a teaching is not contained in Joris and Zhu.

Joris teaches that the *Bacillus licheniformis* protein BLAR-CTD is a water-soluble penicillin-binding protein. This reference is concerned with the expression of BLAR-CTD in *Escherichia coli* and is completely silent about this protein's binding specificities. The same holds true for the Zhu reference. Zhu teaches that B1aR has homology with the OXA-2 β-lactamase *of Salmonella typhimurium* and that BlaR forms a stable complex with β-lactam. The stability is not quantified and not compared to the stability of complexes between β-lactam and binding proteins

from other microorganisms. Further, these documents do not provide any information on the kinetics of the complex formation.

Therefore, neither Zhu nor Joris teach or suggest the superior qualities of *Bacillus licheniformis* proteins in terms of binding velocity and sensitivity when used in detecting antibiotics with a β-lactam ring.

Thus, a person of ordinary skill in the art would not have found any motivation in view of the prior art of record to substitute Piasio's preferred *Bacillus stearothermophilus* proteins with the *Bacillus licheniformis* proteins described in Zhu or Joris to obtain the excellent properties of the present inventive test method.

Furthermore, **the combined teachings of the cited references fail to suggest that use of a β-lactam receptor obtained from *Bacillus licheniformis* will provide an unexpectedly superior method for detecting antibiotics containing a β-lactam ring**. Evidence of the present inventive method's unexpected results of, e.g., sensitivity and rapidity, can be found in the examples disclosed in the present specification, such as, in Example 1 on page 16, lines 8-13.

Consequently, the prior art of record does not teach or suggest the present inventive method of detecting antibiotics containing a β-lactam ring and therefore, the instant rejection should be withdrawn.

In view of the forgoing remarks, it is respectfully submitted that the present application is in condition for allowance. Accordingly, favorable reconsideration and a prompt Notice of Allowance is respectfully solicited.

If the Examiner has any questions regarding this request for consideration, the application in general, or has any suggestions for placing the application in condition for allowance, the Examiner is respectfully requested to call the undersigned at the number listed below.

Respectfully submitted,

Jacques DEGELAEN et al.

By: _____
Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Applicants

JJF/WMC/jlw
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
November 30, 2001